

PREVENTION. HOW MUCH HARM? HOW MUCH BENEFIT?

3. PHYSICAL, PSYCHOLOGICAL AND SOCIAL HARM

Kenneth G. Marshall, MD, CCFP, FRCPC

Abstract • Résumé

Harm caused by preventive programs may be physical, psychological, social or, if informed consent has not been obtained, ethical. Adverse effects of preventive screening programs may occur at any of the three levels of the "screening cascade": the screening procedure itself, the investigation of abnormal results of screening tests or the treatment of detected abnormalities or diseases. The greatest harm occurs at the second and third levels. Examples of procedures that may cause physical harm are venipuncture, mammography, colonoscopy, breast biopsy, transrectal ultrasonography, prostate biopsy, weight-reducing and cholesterol-lowering diets and radical prostatectomy. The psychological and social harm of preventive programs involves anticipated discomfort or perception of adverse effects of preventive interventions, unpleasant interactions with health care workers, time required for preventive programs, excessive overall awareness of health, anxiety over the results of a screening test, implications of a positive screening test, consequences of being labelled as "sick" or "at risk," psychopathologic effects induced directly by preventive programs and, in the case of a false-negative test result, false assurance of disease-free status. Since the positive predictive value of screening tests in the general population is always low, most abnormal test results are "false-positive;" these engender a great deal of psychological distress among patients.

Les préjudices causés par les programmes de prévention peuvent être de nature physique, psychologique ou sociale ou, si l'on n'a pas obtenu de consentement éclairé, éthique. Les programmes de dépistage préventif peuvent avoir des effets indésirables à l'un ou l'autre des trois niveaux de la «cascade du dépistage»: la procédure de dépistage même, l'analyse des résultats anormaux des tests de dépistage ou le traitement des anomalies ou des maladies détectées. Le préjudice le plus grave se produit aux deuxième et troisième niveaux. La ponction veineuse, la mammographie, la colonoscopie, la biopsie du sein, l'ultrasonographie transrectale, la biopsie de la prostate, les régimes amaigrissants et hypocholestérolémians et la prostatectomie radicale sont des exemples d'interventions qui peuvent causer des préjudices physiques. Les préjudices psychologiques et sociaux des programmes de prévention comportent l'inconfort anticipé ou la perception d'effets indésirables d'interventions préventives, des interactions désagréables avec des travailleurs de la santé, le temps nécessaire aux programmes de prévention, la sensibilisation globale excessive à la santé, l'anxiété suscitée par l'attente des résultats d'un test de dépistage, les répercussions d'un test de dépistage qui donne des résultats positifs, les conséquences d'être reconnu comme personne «malade» ou «à risque», les effets psychopathologiques provoqués directement par les programmes de prévention et, dans le cas de résultats d'analyse faussement négatifs, la fausse garantie d'absence de maladie. Comme la valeur prédictive positive des tests de dépistage dans la population générale est toujours faible, la plupart des résultats de tests anormaux sont «faussement positifs» et engendrent beaucoup de détresse psychologique chez les patients.

For patients and physicians to decide whether a specific patient should participate in a preventive program, they must know not only whether the program has proven benefits and how great these benefits are, but

also whether there are associated adverse effects, how serious they are and how often they occur. The previous two articles in this series dealt with some of the pitfalls in determining the significance or even the presence of

Dr. Marshall is associate professor of family medicine, McGill University, Montreal, Que.

Previous articles in this series have appeared in the May 15 and June 15 issues of CMAJ. The last article will appear in the Aug. 15 issue.

Reprint requests to: Dr. Kenneth G. Marshall, Department of Family Medicine, McGill University, 517 Pine Ave. W, Montreal QC H2W 1S4; fax 514 398-4202

© 1996 Canadian Medical Association (text and abstract/résumé)

clinically significant benefits from reading the medical literature. This article reviews some of the ways in which preventive programs may cause harm, and the final article of the series will discuss clinical guidelines for prevention and the ethical norms of prevention.

The harm caused by prevention has received much less attention than its benefits. No one wants to hear bad news. Physicians may have already decided that the benefits outweigh any disadvantages, or they may be afraid that patients will not participate in preventive programs if they are aware of the potential harm. In many instances, detrimental effects are minimal, but that should not stop physicians or their patients from being aware of them.

The types of possible harm to patients participating in preventive programs may be classified as physical, psychological, social or, if informed consent has not been obtained, ethical. Many of these adverse sequelae occur during screening or case-finding programs and result from the "screening cascade," or the series of interventions involved in such programs.¹ The "screening cascade" consists of three levels: the screening process itself, the investigation of detected abnormalities and the management of identified disorders. Although adverse effects occur at all levels, the more serious ones are usually found at the second and third levels (Table 1).

Table 1: Potential harm at the three levels of the "screening cascade"

Level of screening cascade	Type of harm, examples
Screening process	<p>Physical</p> <p>Discomfort resulting from venipuncture or breast compression during mammography</p> <p>Syncope resulting from venipuncture</p> <p>Psychological and social</p> <p>Anxiety over anticipated adverse effects of procedures and over test results</p> <p>Excessive awareness of health</p>
Investigations of abnormal results	<p>Physical</p> <p>Pain and complications of breast biopsy or colonoscopy</p> <p>Psychological and social</p> <p>Anxiety induced by positive results</p> <p>False reassurance from false-negative results</p>
Treatment of detected abnormalities or diseases	<p>Physical</p> <p>Adverse reactions to lipid-lowering drugs or hormone-replacement therapy</p> <p>Impotence, incontinence or death resulting from radical prostatectomy</p> <p>Psychological</p> <p>Distress resulting from actual or anticipated physical harm</p>

A detrimental aspect of any preventive program is its cost to society;²⁻⁸ the money spent on prevention is not available for other uses. The subject of such opportunity costs is an important one, but it is beyond the scope of this series. Instead, I will adopt the perspective of the physician and patient in an office setting, and I will deal with the balance of the benefits and harm of specific preventive programs for particular patients without considering the costs to society as a whole.

The fact that this article deals exclusively with the adverse effects of prevention does not imply that such programs should be eschewed; on the contrary, the harm-to-benefit ratio has to be weighed by physicians and patients, and specific decisions must be made for each program and each patient. This will be discussed further in the final article in this series.

PHYSICAL HARM

DUE TO A SCREENING PROCESS

At the first level of the screening cascade, mammography and venipuncture often cause minor discomfort. In one study, 35% of women stated that mammography caused physical discomfort and 6% described it as painful.⁹ Complications of venipuncture are few and generally innocuous. In a study of 4050 venipunctures, minor bruising or hematoma resulted from 12.3% of procedures, diaphoresis with hypotension from 2.6% and syncope from less than 1%.¹⁰ More serious sequelae of venipuncture include peripheral nerve injury and causalgia,¹¹ asystole,¹² anemia¹³ and needle-stick injuries to those drawing the blood.¹⁴

DUE TO INVESTIGATION OF ABNORMAL RESULTS

Three procedures often used in the investigation of abnormal results of screening tests are colonoscopy, breast biopsy and prostate biopsy.

Colonoscopy

Important physical adverse effects of colonoscopy are pain,¹⁵ vasovagal reactions,¹⁶ perforation, hemorrhage and death.^{17,18} Reported rates of major complications after colonoscopy vary, but are typically 1 in 600 for perforation, 1 in 3600 for significant hemorrhage and 1 in 5000 for death.¹⁷

Breast biopsy

Biopsy of suspicious breast abnormalities detected by mammography is usually performed after needle localization of the lesion. Rappaport and associates¹⁹ re-

ported 11 wound infections after 144 consecutive needle-localization biopsies; in another series of 301 biopsies, there were 12 hematomas, 3 abscesses, 1 seroma and 2 wound separations.²⁰ Vasovagal reactions have been reported in 7% and syncope in 1% of patients undergoing needle aspiration or localization of breast lesions.²¹

Prostate biopsy

If the result of screening for prostate cancer by either digital rectal examination or prostate-specific antigen testing is positive, the next step in the "screening cascade" is usually transrectal ultrasonography and needle biopsy of the prostate. A transrectal ultrasonographic examination appears to cause severe discomfort among only 5% of patients,²² whereas the incidence of pain from needle biopsy has been reported to be 8%²² and 31%.²³ Both hematuria and hemospermia occur among more than half of all patients who have a needle biopsy.^{23,24} Infection rates vary from about 1% to 6% but are lower among patients given prophylactic antibiotics.^{22,24} In a very few cases septicemia and even death have been reported.²⁵ Acute urinary retention is a rare complication.²³

DUE TO TREATMENT

The most serious harm resulting from preventive programs involves the treatment of detected abnormalities or diseases.

Weight-reducing and cholesterol-lowering diets

Weight-loss diets, whether self-prescribed or prescribed by health care professionals, are probably the most prevalent,²⁶⁻²⁸ expensive and ineffective²⁸ preventive programs in our society. Weight loss is correlated with increased rates of death from all causes and from cardiovascular causes, even when calculations are controlled for existing diseases and cigarette smoking.²⁹⁻³¹ The incidence of cholelithiasis is increased among patients eating very low-energy diets,³² although less stringent diets may not have this effect.³³ High-fibre, low-energy diets have been associated with lower bone density among postmenopausal women, compared with the bone density among control women who were not dieting.³⁴

One of the more serious consequences of weight-loss diets is an increase in the incidence of eating disorders, which have numerous psychological and physical sequelae.³⁵⁻³⁷ The adverse consequences of dieting may even be transmitted from one generation to the next. A group of mothers whose children failed to thrive as a result of food restriction scored much higher on a food-restraint scale than a comparable group of mothers whose chil-

dren did not fail to thrive.³⁸ None of the mothers in either group met the criteria for having an eating disorder. This type of generational effect is also seen on a societal level. One study showed that 72% of US high school children had attempted to diet in the 1 to 2 months before the survey,³⁹ and another study found that even third-grade students had tried dieting.⁴⁰ Although the cultural importance of being thin is undoubtedly a major cause of such behaviour, medical recommendations probably also play a significant role.⁴¹ For example, the consensus conference on lowering blood cholesterol levels, held by the US National Heart, Lung and Blood Institute, issued a statement that all Americans over 2 years of age should reduce their intake of dietary fat.⁴² It has been suggested that such a reduced-fat diet may be insufficient for optimal growth and development in children,⁴¹ although no adverse effects were documented in a 3-year trial involving children 8 to 11 years of age who were fed diets in which only 28% of energy was supplied from fat.⁴³

Cholesterol-lowering drugs

Many drugs are used to lower cholesterol levels in order to prevent coronary artery disease, and each of these drugs has its own spectrum of adverse effects. As well, lowering cholesterol itself may be harmful. Two meta-analyses of controlled trials of cholesterol-lowering diets and drugs found that all of the groups undergoing treatment had a significantly higher rate of death from suicide, accidents and violence.^{44,45} Other studies have shown a correlation between low cholesterol levels and overall death rates,^{46,47} rates of death from injuries and suicide⁴⁸ and rates of attempted suicide.⁴⁹ There is also experimental evidence supporting this connection: one study showed that contact aggression was increased in monkeys fed cholesterol-lowering diets.⁵⁰ One explanation for this effect is that either low cholesterol levels or drugs that lower cholesterol levels tend to induce depression.^{51,52} The issue is controversial because not all workers agree with these findings⁵³ and because one primary-prevention trial of pravastatin⁵⁴ and one secondary-prevention trial of simvastatin⁵⁵ showed no evidence of an increase in violence or suicides in the groups taking the drugs.

Radical prostatectomy

In the United States and Canada, the usual treatment for proven localized prostate cancer is radical prostatectomy. A survey of 2122 patients who underwent this procedure in 484 institutions in the United States in 1990 showed the following complications.⁵⁶ Of the patients, 0.7% died as a result of surgery, 56.6% of those

who were potent before surgery became impotent, 3.6% became completely incontinent, 4.1% required more than two pads daily for incontinence, 11.2% required two pads or less daily and 23.1% had occasional incontinence but did not use pads.⁵⁶

PSYCHOLOGICAL AND SOCIAL HARM

Adverse psychological, social or ethical consequences of preventive programs are listed in Table 2. This is an area of great importance but one in which much more research is needed.^{57,58}

ANTICIPATED DISCOMFORT OR PERCEPTION OF ADVERSE EFFECTS RESULTING FROM PREVENTIVE INTERVENTIONS

Participants in screening programs may have realistic or exaggerated perceptions of the degree of discomfort the interventions will cause. Most people are a little discomfited by the thought of having a venipuncture; for a few, the idea of a needle puncture is truly terrifying.⁵⁹ Some women are embarrassed about exposing their breasts during mammography,⁶⁰ and a few fear that the radiation^{60,61} or breast compression⁶² involved in mammography will cause cancer.

UNPLEASANT INTERACTIONS WITH HEALTH CARE WORKERS

A screening program inevitably exposes the participants to increased contact with a variety of health care workers. If any of these workers is uncommunicative, curt or cold, the interaction is unpleasant for the participants.⁶¹

TIME REQUIRED FOR PREVENTIVE PROGRAMS

Preventive programs place demands on participants' time. An initial visit to a physician's office can take up to half a day when transportation and waiting time are factored in. More time is required if the patient is sent to a test centre for venipuncture or to a radiography facility for a mammogram. If a screening test has a positive result, many hours may be required to comply with further investigations and consultations. All of this is time lost from family commitments, work or play.

In countries such as Canada where the costs of most preventive screening programs are covered by public health insurance, the personal financial costs of screening are usually indirect and are limited to loss of income because of time lost from work. However, even in countries with universal coverage, the often substantial cost of drugs prescribed for prevention may not be covered.⁶³

Table 2: Adverse psychological, social and ethical effects of preventive programs	
Adverse effect	Examples
Anticipated discomfort or perceived adverse effects	Pain from needle puncture for blood tests Pain from breast compression during mammography Fear of radiation from mammography Unpleasantness of diet or exercise
Unpleasant interactions with health care workers	Unpleasantness of dealing with curt or uncommunicative personnel in a mammographic screening centre
Time required	Guilt or anxiety concerning time taken from work or family Decrease in functioning at work or at home
Personal financial costs	Loss of income because of time taken from work Payment for specific investigations or prescriptions
Excessive overall awareness of health	Change in perception of general health resulting from worry over elevated cholesterol level or risk of heart disease, stroke or cancer
Anxiety over the results of a screening test	Specific worry that the result of the screening test will be positive
Implications of a positive result of a screening test	Anxiety over the consequences of having a specific disease Decrease in social functioning because of anxiety and time required for further evaluation
Being labelled as "sick" or at "high risk" because of a positive result of a screening test	Dysthymia due to narcissistic injury Decrease in social functioning
Psychopathologic effects of preventive programs	Eating disorder caused by dieting
False assurance of disease-free status	False sense of security resulting from true-negative or false-negative test result
Failure to obtain informed consent	Loss of autonomy Lack of knowledge of possible adverse effects

EXCESSIVE OVERALL AWARENESS OF HEALTH

In North America there is a great deal of concern about bodily functions and health.^{2,64-67} Two decades ago, Thomas⁶⁴ described Americans as having an unhealthy obsession with health. If anything, the situation has worsened. Phrases such as the "tyranny of health"⁶⁶ and a "death-denying culture"² have been used to describe current attitudes.

Does participating or considering participating in a screening program add to the alarm people already feel about their health? In this area there are fewer data than hypotheses; however, there are reports that such interventions are psychologically stressful^{58,59,68-71} and may lead to "cancerophobia"⁶⁸⁻⁷⁰ and increased concern about heart disease.⁷¹

One could argue that the increased anxiety caused by screening programs is a positive outcome because it stimulates patients to look after their health. It may do so. However, assuming increased anxiety to be desirable is a value judgement in which greater worth is ascribed to preoccupation with and possible improvement in health than to comfortable denial or ignorance. Herein lies a paradox: the more attention and introspection we devote to health, the more we tend to amplify symptoms and to make a negative appraisal of our health.^{67,72-74} In a nutshell, the more concerned we are about our health, the worse we feel.

ANXIETY OVER THE RESULTS OF A SCREENING TEST

An inevitable consequence of participating in a preventive program is a greater awareness and often a greater fear of the disease concerned. This concern is sometimes magnified because the anticipated results are perceived emotionally and in black-and-white terms: "Either my cholesterol level will be normal and I will not have to worry about heart attacks, or it will be elevated and I will suddenly drop dead. Either my mammogram will be normal and I will not have to worry about breast cancer, or it will not be and I will die an agonizing, horrible death." Shades of grey and risk spectrum are not part of most people's conception of illness.⁵⁸ For example, few nonphysicians understand the concept of precancerous conditions such as cervical intraepithelial neoplasia, and, as a result, they tend to view even a mildly abnormal result of a Papanicolaou smear as a diagnosis of cancer.⁷⁵

IMPLICATIONS OF A POSITIVE RESULT OF A SCREENING TEST

A positive result of a screening test leads to a great deal of emotional distress.⁵⁷ In one study, about a quarter of the women who received a letter informing them that their

Papanicolaou smear result was abnormal used phrases such as "stunned," "shocked" or "devastated" to describe their reactions.⁷⁵ Even being informed that the result of a screening test is false-positive does not always eliminate psychological distress.^{58,76-79} Lerman and collaborators⁷⁸ studied the psychological status of a group of women who had received false-positive "high-suspicion" results of mammography. Although these women had known for 3 months that they did not have breast cancer, 47% were anxious about having further mammograms, 41% were worried that they had breast cancer and 17% reported a persistent decrease in their ability to engage in daily activities. Similar evidence of persistent anxiety among women with false-positive results of mammographic screening has also been reported by Gram and Slenker.⁷⁹

Physicians and patients should realize that most positive results of any screening program conducted in the general population are false-positive; the positive predictive value is always low. For example, Mandel and colleagues⁸⁰ found that 97.8% of patients with positive results of stool tests for occult blood did not have colon cancer and that 70% had neither colon cancer nor adenomatous polyps. In a study conducted in Scotland involving 91 028 women screened by mammography, 6667 (7.3%) of the women were recalled for repeat mammography or other investigations and 578 (0.6%) were found to have cancer.⁸¹ For 91.4% of the women who were recalled, the initial mammogram was a false-positive one. Although not all women who are recalled because of an abnormal mammogram find the experience psychologically traumatic, many do.⁸²

BEING LABELLED AS "SICK" OR AT "HIGH RISK"

One of the reported detrimental effects of a positive result of a screening test is that the patient is labelled as "sick." This labelling can cause psychological distress⁸³⁻⁸⁷ and decreased occupational functioning.⁸⁷ Not all studies have documented this phenomenon.⁸⁸ It is thought that this is because more recent investigations have incorporated supportive patient counselling that has effectively counteracted the negative consequences of labelling.^{88,89}

Being labelled as at high risk of a disease produces similar psychological effects. In one study, conducted during a 3-year period, a third of men who had been informed that they were at a high risk of having a heart attack suffered from intrusive thoughts and psychological distress.⁹⁰

PSYCHOPATHOLOGIC EFFECTS INDUCED DIRECTLY BY PREVENTIVE PROGRAMS

Patients who diet, and especially those who go through repeated cycles of dieting ("yo-yo dieting"), have been reported to experience a decrease in life satis-

faction and sexual drive, and an increase in fatigue, irritability and depression.^{91,92} As I noted previously, one of the serious consequences of weight-loss diets is an increase in the incidence of eating disorders, which have psychological and physical sequelae.³⁵⁻³⁷

FALSE ASSURANCE OF DISEASE-FREE STATUS

A negative result of a screening test does not rule out the presence of disease. Such a result may cause a false sense of reassurance, which may, in turn, lead to neglect of other aspects of self-care.^{93,94} True-negative results may also have this effect. For example, a smoker with a normal cholesterol level may feel justified in continuing smoking, or a postmenopausal woman may ignore minor vaginal bleeding because she had a normal result of a Papanicolaou smear.

CONCLUSION

Physicians must be as knowledgeable about the harmful effects of prevention as they are about its benefits; otherwise, they will be incapable of giving their patients a balanced perspective when they discuss the pros and cons of preventive interventions.

References

1. Woolf SH: Public health perspective: the health policy implications of screening for prostate cancer. *J Urol* 1994; 152: 1685-1688
2. Annas GJ: Reframing the debate on health care reform by replacing our metaphors. *N Engl J Med* 1995; 332: 744-747
3. Keeney RL: Decisions about life-threatening risks. *N Engl J Med* 1994; 331: 193-196
4. Butler JA: Prevention may be more expensive than cure. *J R Soc Med* 1993; 86: 341-344
5. Pedersen KM: Economics of cancer screening: total costs and benefits in economic terms. *Eur J Cancer* 1994; 30A: 879-884
6. McCormick J: Health promotion: the ethical dimension. *Lancet* 1994; 344: 390-391
7. Weller D, Moss J, Hiller J et al: Screening for colorectal cancer: What are the costs? *Int J Technol Assess Health Care* 1995; 11: 26-39
8. Mason JM, Wakeman AP, Drummond MF et al: Population screening for abdominal aortic aneurysm: Do the benefits outweigh the costs? *J Public Health Med* 1993; 15: 154-160
9. Rutter DR, Calnan M, Vaile MS et al: Discomfort and pain during mammography: description, prediction, and prevention. *BMJ* 1992; 305: 443-445
10. Galena HJ: Complications occurring from diagnostic venipuncture. *J Fam Pract* 1992; 34: 582-584
11. Horowitz SH: Peripheral nerve injury and causalgia secondary to routine venipuncture. *Neurology* 1994; 44: 962-964
12. Lipton JD, Forstater AT: Recurrent asystole associated with vasovagal reaction during venipuncture. *J Emerg Med* 1993; 11: 723-727
13. Dale JC, Pruett SK: Phlebotomy — a minimalist approach. *Mayo Clin Proc* 1993; 68: 249-255
14. Chia HP, Koh D, Jeyaratnam JL: A study of needle stick injuries among medical undergraduates. *Ann Acad Med Singapore* 1993; 22: 338-341
15. Steine S: Which hurts the most? A comparison of pain rating during double-contrast barium enema examination and colonoscopy. *Radiology* 1994; 191: 99-101
16. Hermann LL, Kurtz RC, McKee KJ et al: Risk factors associated with vasovagal reactions during colonoscopy. *Gastrointest Endosc* 1993; 39: 388-391
17. Habr-Gama A, Waye JD: Complications and hazards of gastrointestinal endoscopy. *World J Surg* 1989; 13: 193-201
18. Ransohoff DF, Lang CA, Kuo HS: Colonoscopic surveillance after polypectomy: considerations of cost effectiveness. *Ann Intern Med* 1991; 114: 177-182
19. Rappaport W, Thompson S, Wong R et al: Complications associated with needle localization biopsy of the breast. *Surg Gynecol Obstet* 1991; 172: 303-306
20. Kaelin CM, Smith TJ, Homer MJ et al: Safety, accuracy, and diagnostic yield of needle localization biopsy of the breast performed using local anesthesia. *J Am Coll Surg* 1994; 179: 267-272
21. Helvie MA, Ikeda DM, Adler DD: Localization and needle aspiration of breast lesions: complications in 370 cases. *Am J Roentgenol* 1991; 157: 711-714
22. Hermansson CG, Hugosson J, Pedersen KV: Transrectal ultrasound examination of the prostate: complications and acceptance by patients. *Br J Urol* 1993; 71: 457-459
23. Webb JA, Shanmuganathan K, McLean A: Complications of ultrasound-guided transperineal prostate biopsy. A prospective study. *Br J Urol* 1993; 72: 775-777
24. Gustafsson O, Norming U, Nyman CR et al: Complications following combined transrectal aspiration and core biopsy of the prostate. *Scand J Urol Nephrol* 1990; 24: 249-251
25. Brewster SF, Rooney N, Kabala J et al: Fatal anaerobic infection following transrectal biopsy of a rare prostatic tumour. *Br J Urol* 1993; 72: 977-978
26. Serdula M, Collins ME, Williamson DF et al: Weight control practices of US adolescents and adults: Youth Risk Behavior Survey and Behavioral Risk Factor Surveillance System. *Ann Intern Med* 1993; 119: 667-671
27. Horm J, Anderson K: Who in America is trying to lose weight? *Ann Intern Med* 1993; 119: 672-676
28. Foreyt J, Goodrick K: The ultimate triumph of obesity. [editorial] *Lancet* 1995; 346: 134-135
29. Pamuk ER, Williamson DF, Serdula MK et al: Weight loss and subsequent death in a cohort of US adults. *Ann Intern Med* 1993; 119: 744-748
30. Blair SN, Shaten J, Brownell K et al: Body weight change, all-cause mortality, and cause-specific mortality in the multiple risk factor intervention trial. *Ann Intern Med* 1993; 119: 749-757
31. Reubin A, Muller DC, Sorkin JD: Long-term effects of change in body weight on all-cause mortality. A review. *Ann Intern Med* 1993; 119: 737-743
32. Kamrath RO, Plummer LJ, Sadur CN et al: Cholelithiasis in patients treated with a very-low-calorie diet. *Am J Clin Nutr* 1992; 56 (1 suppl): 255S-257S

33. Thijs C, Knipschild P, Leffers P: Is gallstone disease caused by obesity or by dieting? *Am J Epidemiol* 1992; 135: 274-280
34. Avenell A, Richmond PR, Lean ME et al: Bone loss associated with a high fibre weight reduction diet in postmenopausal women. *Eur J Clin Nutr* 1994; 48: 561-556
35. Wooley SC, Garner DM: Dietary treatments for obesity are ineffective. *BMJ* 1994; 309: 655-656
36. Wadden AT, Stunkard AJ: Psychosocial consequences of obesity and dieting: research and clinical findings. In Stunkard AJ, Wadden TA (eds): *Obesity Theory and Therapy*, 2nd ed, Raven Press, New York, 1993: 163-177
37. Wilson GT: Relation of dieting and voluntary weight loss to psychological functioning and binge eating. *Ann Intern Med* 1993; 119: 727-730
38. McCann JB, Stein A, Fairburn CG et al: Eating habits and attitudes of mothers of children with non-organic failure to thrive. *Arch Dis Child* 1994; 70: 234-236
39. Moses N, Baniliv MM, Lifshitz F: Fear of obesity among adolescent girls. *Pediatrics* 1989; 83: 393-398
40. Maloney MJ, McGuire J, Daniels SR et al: Dieting behavior and eating attitudes in children. *Pediatrics* 1989; 84: 482-487
41. Lifshitz F: Children on adult diets: Is it harmful? Is it healthful? *J Am Coll Nutr* 1992; 11: 84S-90S
42. American Academy of Pediatrics: National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 1992; 89: 525-584
43. Writing Group for the DISC Collaborative Research Group: Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). *JAMA* 1995; 273: 1429-1435
44. Muldoon MF, Manuck SB, Matthews KA: Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990; 301: 309-314
45. Newman TB, Browner WS, Hulley SB: Childhood cholesterol screening: contraindicated. *JAMA* 1992; 267: 100-101
46. Staessen J, Amery A, Birkenhager W et al: Is a high serum cholesterol level associated with longer survival in elderly hypertensives? *J Hypertens* 1990; 8: 755-761
47. Forette B, Tortrat D, Wolmark Y: Cholesterol as a risk factor for mortality in elderly women. *Lancet* 1989; 1: 868-870
48. Linberg C, Råstam L, Gullberg B et al: Low cholesterol concentration and short term mortality from injuries in men and women. *BMJ* 1992; 305: 277-279
49. Golier JA, Marzuk PM, Leon AC et al: Low serum cholesterol level and attempted suicide. *Am J Psychiatr* 1995; 152: 419-423
50. Kaplan JR, Manuck SB, Shively C: The effects of fat and cholesterol on social behavior in monkeys. *Psychosom Med* 1991; 53: 634-642
51. Morgan RE, Palinkas LA, Barrett-Connor EL et al: Plasma cholesterol and depressive symptoms in older men. *Lancet* 1993; 341: 75-79
52. Ketterer MW, Brymer J, Rhoads K et al: Lipid-lowering therapy and violent death: Is depression a culprit? *Stress Med* 1994; 10: 233-237
53. Law MR, Thompson SG, Wald NJ: Assessing possible hazards of reducing serum cholesterol. *BMJ* 1994; 308: 373-379
54. Shepherd J, Cobbe SM, Ford I et al: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333: 1301-1307
55. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. *Lancet* 1994; 344: 1383-1389
56. Murphy GP, Mettlin C, Menck H et al: National patterns of prostate cancer treatment by radical prostatectomy: results of a survey by the American College of Surgeons Commission on Cancer. *J Urol* 1994; 152: 1817-1819
57. Woolf SH, Kamerow DB: Testing for uncommon conditions. The heroic search for positive test results. *Arch Intern Med* 1990; 150: 2451-2458
58. Wardle J, Pope R: The psychological costs of screening for cancer. *J Psychosom Res* 1992; 36: 609-624
59. Lander J: Taking the jab out of needles. *Can Nurse* 1993; 89: 37-40
60. Lerman C, Rimer B, Trock B et al: Factors associated with repeat adherence to breast cancer screening. *Prev Med* 1990; 19: 279-290
61. Baines CJ, To T: Women's attitudes to screening after participation in the national breast screening study: a questionnaire survey. *Cancer* 1989; 65: 1663-1669
62. Blustein J: Medicare coverage, supplemental insurance, and the use of mammography by older women. *N Engl J Med* 1995; 332: 1138-1143
63. Fluvastatin for lowering cholesterol. *Med Lett* 1994; 36: 45-46
64. Thomas L: Notes of a biology-watcher. The health-care system. *N Engl J Med* 1975; 293: 1245-1246
65. White L: How to improve the public's health. *N Engl J Med* 1975; 293: 773-774
66. Fitzgerald FT: The tyranny of health. *N Engl J Med* 1994; 331: 196-198
67. Scrabaneck P: *The Death of Humane Medicine and the Rise of Coercive Healthism*, Crowley Esmonde, Bury Saint Edmunds, England, 1994: 37-41
68. Schmidt JG: The epidemiology of mass breast cancer screening — a plea for a valid measure of benefit. *J Clin Epidemiol* 1990; 43: 215-225
69. Skrabaneck P: False premises and false promises of breast cancer screening. *Lancet* 1985; 2: 316-320
70. Kottke TE, Trapp MA, Fores MM et al: Cancer screening behaviors and attitudes of women in Southeastern Minnesota. *JAMA* 1995; 273: 1099-1105
71. Stoaate HG: Can health screening damage your health. *J R Coll Gen Pract* 1989; 39: 193-195
72. Miller LC, Murphy R, Buss AH: Consciousness of body: private and public. *J Pers Soc Psychol* 1981; 41: 397-406
73. Pennebaker JW: *The Psychology of Physical Symptoms*, Springer-Verlag, New York, 1982: 37-57
74. Barsky AJ: The paradox of health. *N Engl J Med* 1988; 318: 414-418
75. Posner T, Vessey M: *Prevention of Cervical Cancer: the Patient's View*, King's Fund Publishing Office, London, 1988
76. Sorensen JR, Levy HL, Mangione TW et al: Parental response to repeat testing of infants with "false-positive" results in a newborn screening programme. *Pediatrics* 1984; 73: 183-187
77. Burton B, Dillard RG, Clark EN: The psychological impact of false positive elevations of maternal serum alpha-fetoprotein. *Am J Obstet Gynecol* 1985; 151: 77-82

78. Lerman C, Trock B, Rimer BK et al: Psychological and behavioral implications of abnormal mammograms. *Ann Intern Med* 1991; 114: 657-661
79. Gram IT, Slenker SE: Cancer anxiety and attitudes toward mammography among screening attenders, nonattenders, and women never invited. *Am J Public Health* 1992; 82: 249-251
80. Mandel JS, Bond JH, Church TR et al: Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993; 328: 1365-1371
81. Balmy WR, Wilson ARM, Pantoic J et al: Screening for breast cancer. *BMJ* 1994; 309: 1076-1079
82. Roberts MM: Breast screening: Time for a rethink? *BMJ* 1989; 299: 1153-1155
83. Meador CK: The last well person. *N Engl J Med* 1994; 330: 440-441
84. Soghikian K, Hunkeler E: The effect of high blood pressure awareness and treatment on emotional well-being. *Clin Invest Med* 1981; 4: 191-196
85. Monk M: Blood pressure awareness and psychological well-being in the health and nutrition examination survey. *Clin Invest Med* 1981; 4: 183-189
86. Bloom JR, Monterossa S: Hypertension labeling and sense of well-being. *Am J Public Health* 1981; 71: 1228-1232
87. Haynes RB, Sackett DL, Taylor W et al: Increased absenteeism from work after detection and labeling of hypertensive patients. *N Engl J Med* 1978; 299: 741-744
88. Havas S, Reisman J, Hsu L et al: Does cholesterol screening result in negative labeling effects? Results of the Massachusetts Model Systems for Blood Cholesterol Screening Project. *Arch Intern Med* 1991; 151: 113-119
89. Macdonald LA, Sackett DL, Haynes RB et al: Labelling in hypertension: a review of the behavioural and psychological consequences. *J Chron Dis* 1984; 37: 933-942
90. Horowitz M, Hulley S, Alvarez W et al: News of risk for early heart disease as a stressful event. *Psychosom Med* 1980; 42: 37-46
91. Glucksman ML: Psychiatric observations on obesity. *Adv Psychosom Med* 1972; 7: 194-221
92. Brownell KD, Rodin J: Medical, metabolic, and psychological effects of weight cycling. *Arch Intern Med* 1994; 154: 1325-1330
93. Feldman W: How serious are the adverse effects of screening? *J Gen Intern Med* 1990; 5 (suppl 5): S50-S53
94. O'Hagan J: The ethics of informed consent in relation to prevention screening programmes. *N Z Med J* 1991; 104: 121-123

CYTOTEC® (misoprostol) 100 µg 200 µg

THERAPEUTIC CLASSIFICATION Mucosal Protective Agent

INDICATIONS CYTOTEC (misoprostol) is indicated for the prevention of NSAID-induced gastric ulcers. Patients at high risk of developing NSAID-induced complications and who may require protection include: • Patients with a previous history of ulcer disease or a significant gastrointestinal event. • Patients over 60 years of age. • Patients judged to be at risk because of general poor health, severe concomitant medical disease, or patients who are poor surgical risks. • Patients disabled by joint symptoms (e.g., HAQ Disability Index Score >1.5) or those with severe systemic manifestations of arthritis. • Patients taking other drugs known to damage or exacerbate damage to the gastrointestinal tract such as corticosteroids or anticoagulants. • Patients taking a high dosage or multiple NSAIDs, including those available Over-The-Counter. The risk of NSAID-induced complications may be highest in the first three months of NSAID therapy. CYTOTEC is also indicated for the treatment of NSAID-induced gastric ulcers (defined as ≥ 0.3 cm in diameter) and for the treatment of duodenal ulcers.

CONTRAINDICATIONS Known sensitivity to prostaglandins, prostaglandin analogues, or excipients (microcrystalline and hydroxypropyl methylcellulose, sodium starch glycolate and hydrogenated castor oil). Contraindicated in pregnancy. (See CLINICAL PHARMACOLOGY.) Women should be advised not to become pregnant while taking CYTOTEC (misoprostol). If pregnancy is suspected, use of the product should be discontinued.

WARNINGS Women of childbearing potential should employ adequate contraception (i.e., oral contraceptives or intrauterine devices) while receiving CYTOTEC (misoprostol). (See CONTRAINDICATIONS.) **Nursing Mothers:** It is unlikely that CYTOTEC is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, CYTOTEC should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants. **Pediatric Use:** Safety and effectiveness in patients below the age of 18 have not been established.

PRECAUTIONS **Selection of Patients:** Caution should be used when using symptomatology as the sole diagnostic and follow-up procedure, since CYTOTEC (misoprostol) has not been shown to have an effect on gastrointestinal pain or discomfort. Before treatment is undertaken, a positive diagnosis of duodenal ulcer or NSAID-induced gastric ulcer should be made. The general health of the patient should be considered. Misoprostol is rapidly metabolized by most body tissues to inactive metabolites. Nevertheless, caution should be exercised when patients have impairment of renal or hepatic function. (See CLINICAL PHARMACOLOGY: Pharmacokinetics.) **Diarrhea:** Rare instances of profound diarrhea leading to severe dehydration, were it to occur, would be dangerous, should be monitored carefully if CYTOTEC is prescribed. **Use in Elderly or Renally Impaired:** Considerations for Dosage Adjustment: In subjects over 64 years of age or those who are renally impaired the pharmacokinetics may be affected, but not to a clinically significant degree. (See DOSAGE AND ADMINISTRATION.) No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 µg QID) is recommended. **Drug Interactions:** The serum protein binding of misoprostol acid (the active metabolite of misoprostol) was not affected by: indomethacin, ranitidine, dioxigen, phenylbutazone, warfarin, diazepam, mefenidol, propofol, triamterene, cimetidine, acetaminophen, ibuprofen, chlorpromazine, and hydrochlorothiazide. Salicylic acid (300 µg/mL) lowered the protein binding of misoprostol from 84% to 52%; this is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short. In laboratory studies, misoprostol has shown no significant effect on the cytochrome P450-linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system. No drug interactions attributable to misoprostol have been observed to date. (See CLINICAL PHARMACOLOGY.) Some prostaglandins and prostaglandin analogues have the capacity to produce hypotension through peripheral vasodilation. The results of clinical trials to date indicate that CYTOTEC has not produced hypotension at dosages effective in promoting the healing of ulcers. Nevertheless, CYTOTEC should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g., cerebral vascular disease or coronary artery disease. Epileptic seizures have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral. Therefore, misoprostol tablets should be used in known epileptics only when their epilepsy is adequately controlled and then only when expected benefits outweigh potential risks. Symptomatic responses to CYTOTEC do not preclude the presence of gastric malignancy.

ADVERSE REACTIONS **Gastrointestinal:** In subjects receiving CYTOTEC (misoprostol) 400 or 800 µg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea, abdominal pain and flatulence. The average incidences of these events were 11.4%, 6.8% and 2.9%, respectively. In clinical trials using a dosage regimen of 400 µg bid, the incidence of diarrhea was 12.6%. The events were usually transient and mild to moderate in severity. Diarrhea, when it

occurred, usually developed early in the course of therapy, was self limiting and required discontinuation of CYTOTEC in less than 2% of the patients. The incidence of diarrhea can be minimized by adjusting the dose of CYTOTEC, by administering after food, and by avoiding co-administration of CYTOTEC with magnesium-containing antacids. **Gynecological:** Women who received CYTOTEC during clinical trials reported the following gynecological disorders: spotting (0.7%), cramp (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). **Elderly:** There were no significant differences in the safety profile of CYTOTEC in approximately 500 ulcer patients who were 65 years of age or older, compared with younger patients. Confusion has been reported in a small number of patients in our post marketing surveillance of CYTOTEC. Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving CYTOTEC and may be causally related to the drug: nausea (3.2%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%) and constipation (1.1%). However, there were no clinically significant differences between the incidences of these events for CYTOTEC and placebo.

DOSAGE AND ADMINISTRATION **Treatment and Prevention of NSAID-Induced Gastric Ulcers:** The recommended adult oral dosage of CYTOTEC (misoprostol) for the prevention and treatment of NSAID-induced gastric ulcer is 400 to 800 µg a day in divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate CYTOTEC and NSAIDs are to be taken simultaneously, CYTOTEC should be taken after food. **Duodenal Ulcer:** The recommended adult oral dosage of CYTOTEC (misoprostol) for duodenal ulcer is 800 µg per day for 4 weeks in two or four equally divided doses (i.e., 200 µg qid or 400 µg bid). The last dose should be taken at bedtime with food. Antacid (aluminum based) may be used as needed for relief of pain. Treatment should be continued for a total of 4 weeks unless healing in less time has been documented by endoscopic examination. In the small number of patients who may not have fully healed after 4 weeks, therapy with CYTOTEC may be continued for a further 4 weeks. **Use in Elderly and Renally Impaired:** Consideration for Dosage Adjustment: Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{1/2}$, C_{max} and AUC compared to normals. There was no clear correlation between degree of impairment and AUC. In subjects over 64 years of age the pharmacokinetics may be affected. In both patient groups the pharmacokinetic changes are not clinically significant. No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 µg QID) is recommended.

AVAILABILITY CYTOTEC (misoprostol) 200 µg tablets are white to off-white, scored, hexagonal with SEARLE 146 engraved on one side available in bottles of 120 and 500 tablets. CYTOTEC 100 µg tablets are white to off-white, round tablets with SEARLE engraved on one side and CYTOTEC on the other available in bottles of 100 tablets.

Store below 30°C (86°F).

Pharmacist: Dispense with Patient Insert.

400 Iroquois Shore Road
Oakville, Ontario
L6H 1M5

SEARLE

References: 1. Elliott DP. Annals of Pharmacotherapy 1990;24:954-957. 2. Agrawal NW, et al. Annals of Internal Medicine 1991;115(3):195-200. 3. Cryer B, Feldman M. Arch Intern Med June 1992;152:1145-1153. 4. Fries JF. J. Musculoskeletal Medicine 1991;2:21-28. 5. Gabriel SE, et al. Annals of Internal Medicine 1991;115(10):787-79. 6. CYTOTEC® Product Monograph, Searle Canada Inc. 7. Graham DY, Agrawal NM, Roth SH. The Lancet 1988;2:1277-1280. Product Monograph available upon request.

Proven Protection
CYTOTEC® **B.I.D.**
(misoprostol) 200 µg **WITH FOOD**